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## Title Page

**Title:** Adolescent and parent factors related to fatigue in paediatric multiple sclerosis and chronic fatigue syndrome: a comparative study

**Short running head:** Factors related to fatigue in paediatric MS and CFS

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**Abbreviations:** caMS – children and adolescents with multiple sclerosis; CFQ – Chalder Fatigue Questionnaire, CFS – Chronic Fatigue Syndrome; MS – multiple sclerosis, PedsQL-MFS – Paediatric Quality of Life Inventory – Multidimensional Fatigue Scale

**Declaration of Interest:** None

## Abstract

**Background:** Fatigue is a disabling, poorly understood symptom in children and adolescents with multiple sclerosis (caMS), for which effective treatments are lacking. In paediatric Chronic Fatigue Syndrome (CFS), effective psychological interventions have been developed based on psychosocial factors associated with fatigue. This study aimed to identify potentially modifiable factors of fatigue in caMS by comparing caMS, adolescents with CFS, healthy adolescents and their parents on measures of fatigue, psychosocial factors, and neurocognitive functioning.

**Methods:** 175 participants including 30 caMS (15 fatigued, 15 non-fatigued), 30 adolescents with CFS, 30 healthy controls, and their parents were compared on measures of self- and parent-reported fatigue, adolescent and parent cognitive behavioural responses to symptoms, sleep, psychological difficulties, parental distress and objectively measured neurocognitive functioning.

**Results:** Fatigue severity, functional impairment and cognitive behavioural responses to symptoms were equivalent in fatigued caMS and adolescents with CFS, and were significantly higher than in healthy controls and non-fatigued caMS. Neurocognitive functioning was impaired in both caMS groups, but was normal in adolescents with CFS and healthy controls. No between-group differences were identified in adolescent sleep behaviour or psychological difficulties. Parents of all illness groups had more unhelpful cognitions than parents of healthy controls. Psychological distress was elevated in parents of both fatigued groups.

**Conclusions:** Fifty percent of caMS reported clinically significant fatigue. Similarities between adolescent and parent cognitive behavioural factors in fatigued caMS and adolescents with CFS suggest important potential targets for intervention. Both fatigued and non-fatigued caMS had cognitive difficulties, suggesting that fatigue may need targeted intervention.



**Keywords:** Adolescence; Chronic Fatigue Syndrome; Fatigue; Multiple Sclerosis; Paediatric

## Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, typically diagnosed in young adults (Murray, 2006). With a UK incidence rate of <1 in 100,000, paediatric MS is rare (Absoud et al., 2013). Children and adolescents with MS (caMS) experience similar physical symptoms to adults with MS, including sensory and motor impairments, visual disturbances and bladder and bowel dysfunction (Compston & Coles, 2008). For caMS, however, physical symptoms tend to be much less severe than in adults with MS. Cognitive symptoms cause greater disturbance in caMS as deficits in memory, language and attention and processing speed can have potentially long-term, serious consequences for school performance and academic attainment (Amato et al., 2010). Fatigue is also one of the most pervasive and disabling symptoms of MS (Giovannoni, 2006). In caMS, fatigue levels ranging from 9-76% have been reported in studies carried out across Europe and North America, with no clear reason for variability in reports. (Carroll, Chalder, Hemingway, Heyman, & Moss-Morris, 2016b).

Despite its impact, fatigue is a poorly understood symptom in paediatric MS, for which effective treatments are lacking. A recent systematic review of 12 studies that explored factors associated with fatigue in caMS indicated that fatigue is unrelated to clinical or demographic factors, but is associated with psychosocial factors including depressed mood, impaired school performance and lower quality of life. Some evidence also suggested that fatigued caMS may have impaired performance on some neurocognitive tasks (Carroll et al., 2016b). This systematic review highlighted the paucity of psychosocial factors explored in the context of fatigue, with most studies focusing on associations between fatigue and depressed mood. Few studies have investigated other potentially modifiable psychosocial factors related to fatigue, such as cognitive and behavioural responses to symptoms e.g. catastrophising, symptom focusing and avoidance behaviour. Additionally, no previous studies have compared psychosocial factors or neurocognitive functioning between fatigued and non-fatigued caMS.

To improve our understanding of fatigue in paediatric MS, it would be helpful to learn from other conditions where fatigue is better understood. However, despite a growing body of evidence that fatigue is one of the most universally experienced symptoms in paediatric long-term conditions, research on factors related to fatigue in this context is still relatively

sparse (Crichton, Knight, Oakley, Babl, & Anderson, 2015). Some exceptions to this are cancer, juvenile idiopathic arthritis, and Chronic Fatigue Syndrome (CFS) where a wider body of evidence has contributed to an improved understanding of fatigue. In cancer and rheumatoid arthritis, the aetiology of fatigue appears to be both treatment and disease related (Armbrust et al., 2016; Nunes et al., 2018) but in MS fatigue has not been linked to treatment. This paper therefore draws largely on the adult MS and adolescent Chronic Fatigue Syndrome (CFS) literature, where empirically based overlapping biopsychosocial cognitive-behavioural models of fatigue have been developed.

Adolescent Chronic Fatigue Syndrome (CFS), an illness characterised by persistent, disabling mental and physical fatigue (Lievesley, Rimes, & Chalder, 2014; Moss-Morris et al., 2012). These models posit that fatigue is triggered by biological factors, then perpetuated by the interaction between these factors and individuals' cognitive, behavioural and emotional responses (van Kessel & Moss-Morris, 2006). Cognitive responses such as perceiving fatigue as an uncontrollable symptom, and behavioural responses such as excessive activity when symptoms abate and limited activity when they reappear, have been associated with increased fatigue. The reciprocal relationship between fatigue and emotional factors such as depressed mood and anxiety may also contribute to persistent fatigue (Jopson & Moss-Morris, 2003; Knoop, van Kessel, & Moss-Morris, 2012; Lievesley et al., 2014; Skerrett & Moss-Morris, 2006). It is worth noting that a recent meta-analysis showed that these perpetuating factors appear to be transdiagnostic in fatigue across a wide range of medical conditions (Menting et al., 2018).

The family-focused cognitive behavioural model of adolescent CFS highlights the role of parental factors such as maternal distress and parents' cognitive and behavioural responses to their child's symptoms in perpetuating fatigue (Lievesley et al., 2014). Parents' perceptions of their child's vulnerability, parental overprotection and parental distress have also been associated with child adjustment, increased symptoms, and school absence across a range of conditions, yet these factors have seldom been explored in paediatric MS research (Lievesley et al., 2014; Palermo, Valrie, & Karlson, 2014; Spurrier et al., 2000). Some previous studies have assessed self- and parent-reports of children's fatigue. Findings regarding concordance between self- and parent-reports have been mixed, demonstrating the need to collect multi-rater perspectives to get a clearer picture of children's fatigue (Carroll et al., 2016b).

In adult MS and adolescent CFS, cognitive behavioural therapy (CBT), which in this context helps people to identify and subsequently adapt their thoughts, behaviours and emotions that contribute to fatigue, has been effective in reducing fatigue severity and impact in clinical trials (Asano, Berg, Johnson, Turpin, & Finlayson, 2015; Chalder, Deary, Husain, & Walwyn, 2010; Nijhof, Bleijenberg, Uiterwaal, Kimpen, & van de Putte, 2012; van Kessel et al., 2008). As parental factors may contribute to fatigue, adolescent CFS research has noted the importance of involving parents in interventions for fatigue (Chalder et al., 2010). No such interventions exist for caMS, thus research in this area is warranted.

A recent qualitative study suggested that caMS with fatigue have similar cognitive and behavioural responses to symptoms to those previously identified in adolescent CFS, such as perceiving fatigue as an uncertain, uncontrollable symptom, and engaging in "all-or-nothing" patterns of behaviour and daytime napping (Carroll, Chalder, Hemingway, Heyman, & Moss-Morris, 2016a; Lievesley et al., 2014). To date, much of the literature on psychosocial factors related to fatigue in paediatric conditions has been carried out in the context of CFS (Crichton et al., 2015). As paediatric fatigue is currently best understood from a biopsychosocial perspective in the context of adolescent CFS, assessing similarities and differences in fatigue and psychosocial factors between caMS and adolescents with CFS may offer insight into fatigue-related factors in paediatric MS. If similar psychosocial factors are associated with fatigue in caMS and adolescents with CFS, this may facilitate the development of tailored interventions for caMS with fatigue, based on psychological therapies that have been effective in treating adolescent CFS.

Additionally, as previous studies have reported mixed findings on the relationship between fatigue and neurocognitive functioning in caMS, it would also be useful to compare neurocognitive functioning between groups to assess whether impairments in neurocognitive functioning differ in those with and without fatigue. As neurocognitive impairment is likely an indicator of greater disease severity in paediatric MS (Julian et al., 2013; MacAllister et al., 2005), comparing fatigued and non-fatigued patients on measures of neurocognitive functioning may provide insight into whether fatigue is related to disease severity in paediatric MS. As an exploratory study, the overall aims were to: :

1. Compare fatigue, psychosocial factors previously associated with fatigue, and neurocognitive functioning across four groups (a) caMS with fatigue, (b) caMS without fatigue, (c) adolescents with CFS, and (d) adolescents without a chronic illness.

2. Compare parent reports of offspring fatigue across the four groups, and investigate the level of agreement between adolescent- and parent-reported fatigue.

3. Compare parents' cognitive and behavioural responses to their child's symptoms and parental distress across the four groups.

Based on previous literature in adult MS and adolescent CFS, our specific hypotheses were:

1. There would be no differences in fatigue, functional impairment or cognitive and behavioural responses to symptoms between caMS with fatigue and adolescents with CFS, and both fatigued groups would have greater fatigue, higher functional impairment, and more unhelpful cognitive and behavioural responses to symptoms than caMS without fatigue and healthy controls.
2. There would be no differences in parent-reported fatigue, parent-reported cognitive and behavioural responses to symptoms, and parental distress between caMS with fatigue and adolescents with CFS. Both fatigued groups would have higher parent-reported fatigue, more unhelpful cognitive and behavioural responses to symptoms, and higher parental distress than caMS without fatigue and healthy controls.

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## Methods

### *Design*

An observational cross-sectional comparative study design was used.

*Participants*

CaMS aged 6-18 with a confirmed MS diagnosis were included (Polman et al., 2011). Children and adolescents with CFS were included if they were aged 6-18 and met the Oxford (Sharpe et al., 1991) or CDC (Fukuda et al., 1994) criteria for CFS, but with at least three months' duration rather than six, following National Institute for Health and Care Excellence guidelines (NICE, 2007). Healthy controls aged 6-18 with no previous or current physical or mental illnesses were included. Primary caregivers of adolescents in all groups were included.

*Materials*

**Demographic and clinical data:** Standard demographic details were collected from all participants. Clinical information collected from caMS included age at onset, disease duration, treatment type, and treatment duration.

*Child and adolescent measures*

**Fatigue "case-ness":** The 11-item version of the Chalder Fatigue Questionnaire (CFQ) using bimodal [0, 0, 1, 1] scoring was used to divide caMS into "fatigued" and "non-fatigued" groups, using a cut-off of 4. This cut-off was chosen as a score of 4 or above indicates clinically significant fatigue. This measure has been shown to be valid and reliable in adult populations (Chalder et al., 1993), and has been used widely in the paediatric literature (Bould, Collin, Lewis, Rimes, & Crawley, 2013; Chalder, Tong, & Deary, 2002; Crawley, Hunt, & Stallard, 2009).

**Fatigue severity** was measured using the Paediatric Quality of Life Inventory – Multi-dimensional Fatigue Scale (PedsQL-MFS). This is a valid and reliable measure of fatigue with three subscales: general, cognitive and sleep/rest fatigue, scored on a 5-point Likert scale (0, never to 4, always) and transformed to a 100-point scale. Lower scores indicate higher fatigue (Varni, Burwinkle, & Szer, 2004).

**Functional impairment** was measured using the adolescent version of the five-item Work and Social Adjustment Scale (WSAS), which has previously been used in the adolescent

fatigue literature. The scale measures impairment in school, social and private leisure activities on an eight-point scale (Chalder et al., 2010; Mundt, Marks, Shear, & Greist, 2002). Work was replaced with school/college.

**School attendance rate** was measured by dividing actual by expected attendance hours.

**Cognitive and behavioural responses to symptoms** were measured using the Cognitive and Behavioural Responses to Symptoms Questionnaire (CBRQ), which measures fear avoidance, symptom catastrophising, damage beliefs, embarrassment avoidance, all-or-nothing behaviour, and avoidance-rest behaviour. The CBRQ has previously been shown to predict ongoing symptom experience, fatigue and impairment in MS and CFS (Knoop et al., 2012; Skerrett & Moss-Morris, 2006). It has been validated in adults with CFS (Ryan, Vitoratou, Goldsmith, & Chalder, 2018) and is used clinically with adolescents with CFS.

**Sleep behaviour** was assessed using the Adolescent Sleep Hygiene Scale (ASHS), a reliable 28-item scale that measures positive and inhibitory sleep behaviours on a six-point scale (1 = always, 6 = never). Higher scores indicate better sleep practices (LeBourgeois, Giannotti, Cortesi, Wolfson, & Harsh, 2005; Lewandowski, Toliver-Sokol, & Palermo, 2011).

**Psychological difficulties** were measured using the Strengths and Difficulties Questionnaire (SDQ), which provides a continuous measure of internalising difficulties, encompassing emotional and peer problems, and externalising problems, including behavioural and hyperactivity problems in children and adolescents (Goodman, 2001).

**Neurocognitive functioning** was assessed in children aged 16 or younger using a short-form version of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) (Crawford, Anderson, Rankin, & MacDonald, 2010; Wechsler, 2003) and in adolescents aged 17 or older using the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) (Wechsler, 2014). Both measures provide evaluation of expressive and receptive language, non-verbal reasoning, working memory, and timed visual motor integration. These measures have previously been used in paediatric MS research to capture cognitive impairment and decline (Amato et al., 2008; MacAllister et al., 2005).

*Parent measures*

**Parent-reported fatigue** was assessed using the PedsQL-MFS, parent version.

**Parent cognitive and behavioural responses to symptoms** were assessed using the fear-avoidance, damage beliefs and catastrophising subscales of the CBRQ parent version, which assesses parents' beliefs about their children's symptoms and their management.

**Parental distress** was measured using the General Health Questionnaire (GHQ-12), a 12-item questionnaire that measures general distress levels in adults (Goldberg, 1992).

*Procedure*

Ethical approval was granted by the West London and GTAC NHS Research Ethics Committee [REC Ref: 15/LO/0091], and R&D departments at participating hospitals. CaMS and adolescents with CFS were recruited through NHS specialist paediatric neurology or chronic fatigue services and online advertisements on MS and CFS charity websites. At NHS clinics, eligible participants were identified by a member of the child's clinical team and invited to participate during clinic appointments or by invitation letter. Healthy controls were recruited from schools and through online advertisements. All parents, children and adolescents provided informed consent or assent, where appropriate. Participants completed a battery of self-report questionnaires and had one meeting with a member of the research team to complete the WISC-IV/WAIS-IV, age-dependent. Where caMS had completed a WISC-IV/WAIS-IV as part of routine care in the previous 12 months, scores were taken from patient notes as practice effects invalidate a repeat assessment within a one-year period. Scores are unlikely to change within this time-frame (Wechsler, 2003).

*Analysis*

Statistical analyses were conducted using IBM SPSS version 22. Overall, less than 5% of individual data points were missing, thus missing data were handled using mean imputation. However, approximately 30% of neurocognitive data was missing from the MS and CFS groups, and 15% from healthy controls. The most common reason for non-completion of the WISC-IV/WAIS-IV was participants living too far from London to travel. Descriptive statistics were run to profile groups and, where appropriate, one-way ANOVA or chi-squared tests were performed to identify differences in participant characteristics across groups. When comparing fatigue and psychosocial factors across groups, caMS were grouped as 'fatigued' or 'non-fatigued' using the CFQ. Differences in group means on measures of fatigue, psychosocial factors and neurocognitive functioning were compared using one-way ANOVA,

with post-hoc Tukey tests where the assumption of homogeneity of variances was met, and Welch's ANOVA with Games-Howell post-hoc tests where Levene's test indicated the assumption of homogeneity of variances was violated. Pearson correlations assessed agreement between self- and parent-reported fatigue. To account for multiple comparisons, a significance value of $p < 0.01$ was applied.

## Results

### *Reliability analysis*

All measures demonstrated high reliability in the total sample with α approaching or exceeding .90, except for the Adolescent Sleep Hygiene Scale, which demonstrated good reliability (α = .71).

### *Demographics*

A total of 175 participants were recruited; 30 caMS and 30 of their parents, 30 adolescents with CFS and 28 of their parents, and 30 healthy controls and 27 of their parents. Demographic characteristics of all groups are presented in Tables 1 and 2.

**Table 1**. *Child and adolescent demographics characteristics across groups*

| | MS (n = 30) | CFS (n = 30) | HC (n = 30) | One-way ANOVA or $\chi^2$ tests for group comparisons |
|---|---|---|---|---|
| Age (years), *M* (range) | 15.87 (9.27-18.95) | 15.67 (12.24.18.00) | 15.02 (8.54-18.54) | $F$ (2, 87) = .87, $p$ = .45 |
| Gender (*n* female) | 18 | 21 | 18 | $\chi^2$ (2) = .86, $p$ = .65 |
| Nationality (*n*) | | | | $\chi^2$ (2) = 11.46, $p$ = .003 |
| British | 21 | 30 | 24 | |
| Non-British | 9 | 0 | 6 | |
| Ethnicity (*n*) | | | | $\chi^2$ (2) = 8.75, $p$ = .013 |
| White | 16 | 26 | 23 | |
| Black | 5 | 0 | 1 | |
| Mixed | 3 | 3 | 2 | |
| Asian | 4 | 1 | 4 | |
| Other | 2 | 0 | 0 | |

**Table 2.** *Parent demographics characteristics across groups*

| | MS (n = 30) | CFS (n = 28) | HC (n = 27) | One-way ANOVA or $\chi^2$ tests for group comparisons |
|---|---|---|---|---|
| Age (years), mean (range) | 46.75 (32.70, 65.47) | 48.16 (38.56, 57.81) | 45.06 (34.15, 50.67) | $F$ (2, 82) = 1.60, $p$ = .21 |
| Relationship to child (*n*) | | | | $\chi^2$ (4) = .43, $p$ = .43 |
| Mother | 25 | 27 | 25 | |
| Father | 5 | 1 | 2 | |
| Nationality (*n*) | | | | $\chi^2$ (2) = 11.09, $p$ = .004 |
| British | 20 | 28 | 22 | |
| Non-British | 10 | 00 | 5 | |
| Ethnicity (*n*) | | | | $\chi^2$ (2) = 16.51, $p$ = .09 |
| White | 18 | 26 | 23 | |
| Black | 6 | 1 | 2 | |
| Mixed | 3 | 0 | 0 | |
| Asian | 1 | 1 | 2 | |
| Other | 2 | 0 | 0 | |

*Grou*p *Comparisons*

When dividing caMS into 'fatigued' and 'non-fatigued' groups on the CFQ, 50% scored ≥4, resulting in a sample size of 15 in each group. When comparing fatigued and non-fatigued caMS on MS-related factors, there were no significant differences in age at onset, illness duration, number of relapses, or treatment duration (Table 3). Means, standard deviations and results of one-way or Welch's ANOVA for group comparisons in adolescent outcomes are shown in Table 4, and parent outcomes in Table 5. Post-hoc test results for all between group comparisons are reported in supplementary materials 1, and key findings are reported in the main text.

**Table 3.** *Clinical characteristics of MS fatigued and non-fatigued groups*

| Variable | MS Fatigued (n = 15) | MS Non-fatigued (n = 15) | Independent samples t-test to compare means |
|---|---|---|---|
| Age at MS onset (mean ± SD) | 12.97 ± 4.32 | 12.62 ± 3.47 | $t$ (28) = .25, $p$ = .81 |
| Illness Duration months (mean ± SD) | 3.29 ± 3.76 | 2.87 ± 2.27 | $t$ (28) = .37, $p$ = .71 |
| Relapse in past year (mean ± SD) | 1.33 ± 1.63 | 1.27 ± 1.44 | $t$ (28) = .12, $p$ = .91 |
| Treatment type | | | |
| Injectable treatment (*n*) | 5 | 10 | |
| Oral treatment (*n*) | 5 | 3 | |
| Monthly Infusion (*n*) | 1 | 2 | |
| Vitamin D (*n*) | 3 | | |
| None (*n*) | 1 | | |
| Treatment duration months (mean ± SD) | 9.38 ± 7.54 | 13.63 ± 11.86 | $t$ (19) = -1.01, $p$ = .33 |

*Fatigue severity and functional impairment*

One-way ANOVA demonstrated a significant main effect of group across all self- and parent- measures of fatigue severity (Tables 4 and 5). Post-hoc tests showed that self- and parent-reported general, sleep and cognitive fatigue were significantly higher in both fatigued groups than in both non-fatigued groups (all $p$ <.001), except for parent-reported fatigue in caMS. Parent-reported general and sleep fatigue were significantly higher in fatigued caMS than in non-fatigued caMS (both $p$ = .002), but parent-reported cognitive fatigue did not differ between these groups (figure 1). There were no significant differences between fatigued caMS and adolescents with CFS on any measure of self- or parent-reported fatigue severity (supplementary materials 1). All parent and self-reported fatigue variables were significantly correlated: general fatigue ($r$ = .78, $p$ < .001), sleep fatigue ($r$ = .80, $p$ < .001) and cognitive fatigue ($r$ = .71, $p$ = .001).

There was a significant main effect of group on functional impairment. Fatigued caMS reported significantly greater functional impairment than healthy controls ($p$ = .001). Adolescents with CFS reported significantly greater functional impairment than healthy controls ($p$ < .001) and non-fatigued caMS ($p$ < .001). There were no significant differences between non-fatigued caMS and fatigued caMS or healthy controls (Supplementary materials 1).

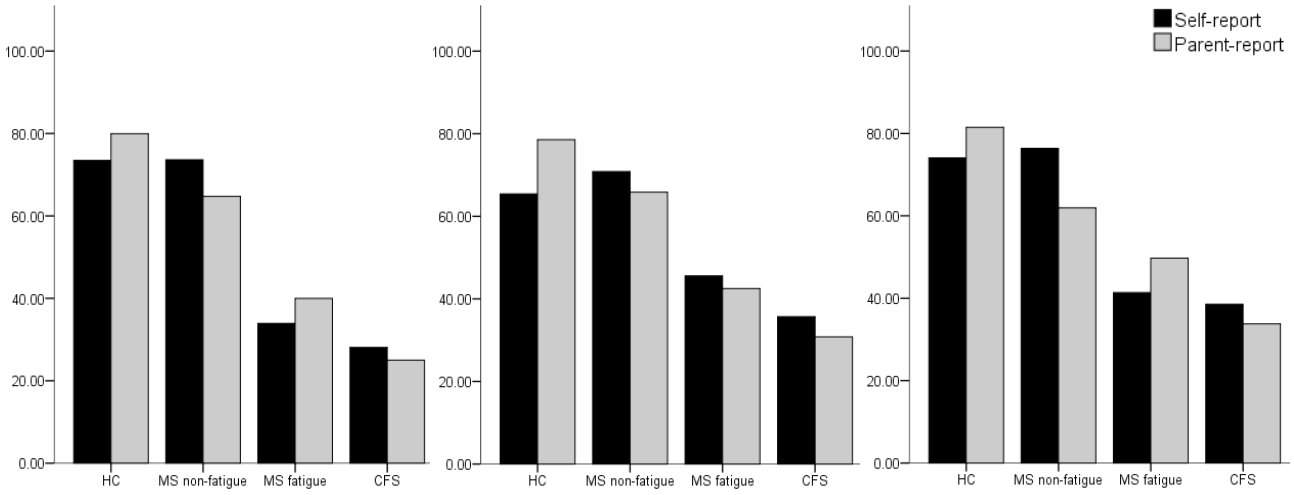


*Figure 1.* Bar charts showing group differences in mean self- and parent-reported fatigue scores on the general, sleep and cognitive fatigue subscales of the PedsQL-MFS. Note: lower scores indicate higher fatigue. CFS = chronic fatigue syndrome, HC = healthy controls.

**Table 4.** *Between group comparisons across self-report measures of fatigue and psychosocial factors*

| | Group means and standard deviations *M* (SD) | | | | One-way or Welch ANOVA for group comparisons |
|---|---|---|---|---|---|
| | MS-fatigue (n = 15) | MS non-fatigue (n=15) | CFS (n = 30) | HC (n = 30) | |
| **Self-reported fatigue severity** | | | | | |
| Self-reported general fatigue | 33.89 (18.15) | 73.61 (13.24) | 26.81 (19.07) | 74.17 (17.38) | *F* (3) = 49.66, *p* < .001 |
| Self-reported sleep fatigue | 45.56 (20.80) | 70.83 (13.55) | 35.28 (16.15) | 66.67 (18.83) | *F* (3) = 22.33, *p* < .001 |
| Self-reported cognitive fatigue | 41.39 (28.28) | 76.39 (23.61) | 37.08 (18.16) | 74.03 (21.54) | *F* (3) = 20.39, *p* < .001 |
| **Functional impairment** [a] | 16.80 (11.66) | 6.47 (5.74) | 23.80 (10.09) | 1.67 (3.79) | *F* (3) = 46.06, *p* < .001 |
| **School attendance rate** [a] | .76 (.24) | .95 (.12) | .62 (.34) | .97 (.12) | *F (3)* = 10.53, *p* < .001 |
| **Sleep Behaviour** | | | | | |
| Physiological | 4.67 (.82) | 4.83 (.65) | 4.90 (.64) | 4.77 (.63) | *F* (3) = .418, *p* = .741 |
| Behavioural arousal | 4.04 (1.05) | 3.42 (1.19) | 3.54 (.92) | 3.82 (1.22) | *F* (3) = 1.14, *p* = .337 |
| Cognitive/emotional [a] | 3.90 (.96) | 4.61 (.98) | 4.09 (.97) | 4.58 (.63) | *F* (3) = 3.30, *p* = .031 |
| Sleep environment [a] | 4.96 (1.09) | 5.28 (.55) | 5.55 (.54) | 5.47 (.61) | *F* (3) = .174, *p* = .175 |
| Sleep stability | 3.02 (1.05) | 3.38 (1.50) | 3.59 (1.32) | 3.26 (1.03) | *F* (3) = .81, *p* = .493 |
| Daytime sleepiness [a] | 4.33 (1.30) | 5.40 (.66) | 4.80 (1.44) | 5.60 (.78) | *F* (3) = 5.44, *p* = .003 |
| **CBRQ** | | | | | |
| Fear avoidance | 12.80 (5.25) | 9.60 (5.01) | 14.33 (3.58) | 9.80 (5.30) | *F* (3) = 5.96, *p* = .001 |
| Catastrophising | 7.13 (4.47) | 4.80 (4.66) | 8.23 (3.46) | 3.00 (3.01) | *F* (3) = 10.91, *p* < .001 |
| Damage beliefs | 11.13 (3.62) | 9.13 (3.40) | 11.80 (3.03) | 7.82 (3.97) | *F* (3) = 7.23, *p* < .001 |
| Embarrassment avoidance [a] | 11.63 (7.96) | 6.00 (4.39) | 11.77 (5.73) | 5.41 (5.00) | *F* (3) = 8.76, *p* < .001 |

**Table 4.** *Between group comparisons across self-report measures of fatigue and psychosocial factors*

| | Group means and standard deviations *M* (SD) | | | | One-way or Welch ANOVA for group comparisons |
|---|---|---|---|---|---|
| | MS-fatigue (n = 15) | MS non-fatigue (n=15) | CFS (n = 30) | HC (n = 30) | |
| Symptom focusing | 12.07 (4.96) | 8.67 (4.70) | 14.23 (4.80) | 7.28 (6.24) | *F* (3) = 9.55, *p* < .001 |
| All-or-nothing behaviour | 10.07 (6.41) | 5.53 (3.83) | 9.60 (5.56) | 4.03 (4.34) | *F* (3) = 8.22, *p* < .001 |
| Avoidance-rest behaviour [a] | 11.33 (5.39) | 8.00 (5.86) | 12.90 (4.88) | 7.38 (7.50) | *F* (3) = 4.95, *p* = .005 |
| **Psychological difficulties** | | | | | |
| Internalising problems [a] | 7.60 (4.74) | 3.80 (2.83) | 6.48 (2.78) | 3.56 (3.45) | *F* (3) = 5.27, *p* = .005 |
| Externalising problems [a] | 6.00 (5.31) | 3.93 (2.99) | 6.22 (2.84) | 4.32 (2.84) | *F* (3) = 2.52, *p* = .079 |
| **Cognitive Functioning** | **(n = 8)** | **(n = 11)** | **(n = 22)** | **(n = 25)** | |
| Verbal Comprehension | 101.57 (11.52) | 91.82 (15.30) | 103.95 (10.25) | 109.12 (12.70) | *F* (3) = 5.12, *p* = .003 |
| Perceptual Reasoning | 98.43 (11.67) | 89.36 (12.82) | 101.86 (7.69) | 102.44 (10.21) | *F* (3) = 4.84, *p* = .004 |
| Working Memory | 91.14 (18.01) | 95.91 (9.48) | 99.41 (10.42) | 104.84 (14.24) | *F* (3) = 2.67, *p* = .053 |
| Processing Speed [a] | 84.14 (17.56) | 83.64 (21.97) | 99.91 (9.13) | 106.88 (10.78) | *F* (3) = 6.81, *p* = .003 |
| Full Scale IQ | 92.14 (14.69) | 86.91 (16.20) | 102.45 (9.86) | 107.72 (10.74) | *F* (3) = 9.09, *p* < .001 |

Note: On the PedsQL-MFS, higher scores indicate lower fatigue and vice versa. [a] equal variances not assumed – results of Welch ANOVA presented; Abbreviations: MS = multiple sclerosis, CFS = chronic fatigue syndrome, HC = healthy control, CBRQ = cognitive and behavioural responses to symptoms.

Questionnaire scoring: PedsQL-MFS (fatigue severity): Scored on a 5 point Likert scale and transformed to a 100-point scale where higher scores indicate lower fatigue (i.e. 100 = not at all fatigued); WSAS (functional impairment): scored from 0 to 40, higher scores indicate greater functional impairment; CBRQ (cognitive and behavioural responses to symptoms): Each subscale is scored out of a different total score, where higher scores indicate more unhelpful responses: fear avoidance (0-24), catastrophising (0-16), damage beliefs (0-20), embarrassment avoidance (0-24), symptom focusing (0-24), all-or-nothing behaviour (0-20), avoidance-rest behaviour (0-32); ASHS (Sleep): Each item is scored on a six-point Likert scale, where higher scores indicate better sleep practices.

**Table 5.** *Between group comparisons across parent-report measures of fatigue and parent psychosocial factors*

| | Group means and standard deviations *M* (SD) | | | | One-way or Welch ANOVA for group comparisons |
|---|---|---|---|---|---|
| | MS-fatigue (n = 15) | MS non-fatigue (n=15) | CFS (n = 28) | HC (n = 27) | |
| **Parent-reported fatigue severity** | | | | | |
| Parent-reported general fatigue | 40.00 (21.41) | 64.72 (21.24) | 25.00 (13.18) | 79.94 (19.03) | $F$ (3) = 46.37, $p$ < .001 |
| Parent-reported sleep fatigue | 42.50 (21.66) | 65.83 (17.97) | 30.80 (12.34) | 78.55 (18.62) | $F$ (3) = 39.49, $p$ < .001 |
| Parent-reported cognitive fatigue | 49.72 (31.83) | 61.94 (22.26) | 33.78 (16.41) | 81.48 (15.94) | $F$ (3) = 25.02, $p$ < .001 |
| **Parent CBRQ** | | | | | |
| Parent fear avoidance beliefs | 13.40 (6.61) | 9.95 (2.69) | 15.89 (3.76) | 7.07 (4.36) | $F$ (3) = 19.68, $p$ < .001 |
| Parent catastrophising | 8.60 (3.00) | 6.20 (2.65) | 9.18 (3.67) | 2.67 (3.46) | $F$ (3) = 19.95, $p$ < .001 |
| Parent damage beliefs | 10.73 (3.81) | 11.27 (3.03) | 13.64 (3.18) | 6.67 (3.21) | $F$ (3) = 21.14, $p$ < .001 |
| **Parental Distress** | 15.53 (5.79) | 11.87 (5.01) | 15.68 (5.43) | 10.67 (5.56) | $F$ (3) = 5.02, $p$ = .003 |

Note: On the PedsQL-MFS, higher scores indicate lower fatigue and vice versa. [a] equal variances not assumed – results of Welch ANOVA presented; Abbreviations: MS = multiple sclerosis, CFS = chronic fatigue syndrome, HC = healthy control, CBRQ = cognitive and behavioural responses to symptoms

*School Attendance Rate*

School attendance was high in healthy controls ($M$ = 97%) and non-fatigued caMS ($M$ = 95%), but lower in fatigued caMS ($M$ = 76%) and adolescents with CFS ($M$ = 62%). Welch's ANOVA demonstrated a significant main effect of group on school attendance (Table 4). Post-hoc Games-Howell tests showed significantly lower school attendance in adolescents with CFS than in non-fatigued caMS and healthy controls (both $p < .001$, supplementary materials 1), but showed no other differences between groups.

*Neurocognitive Functioning*

Descriptive statistics indicated that over 90% of healthy controls and over 86% of adolescents with CFS scored within or above average population norms (90-109) on all measures of neurocognitive functioning, with the remainder scoring within the low average range (80-89) (Table 4). CaMS, however, appeared to have impaired performance on all measures, with only 66.7% scoring within or above population norms on verbal comprehension, 55.6% on perceptual reasoning, 61% on working memory, 38.9% on processing speed, and 55.6% on full scale IQ. Processing speed appeared most affected, with 27.8% scoring low average, and 23.3% scoring within the borderline (70-79) or extremely low range ($\leq 69$). Almost 28% of caMS scored within these ranges on full scale IQ, 16.7% on verbal comprehension and working memory, and 11.2% on perceptual reasoning.

One-way ANOVA demonstrated a significant main effect of group on verbal comprehension, perceptual reasoning, processing speed and full-scale IQ (Table 4). Post-hoc Tukey tests showed that non-fatigued caMS had significantly lower verbal comprehension scores than healthy controls ($p = .001$), but there were no other between-group differences on this subtest. Non-fatigued caMS had significantly lower perceptual reasoning scores than adolescents with CFS ($p = .007$) and healthy controls ($p = .004$), and significantly lower full-scale IQ than adolescents with CFS ($p = .004$) and healthy controls ($p < .001$). There were no differences between fatigued and non-fatigued caMS on any measure of neurocognitive functioning. Post-hoc Games-Howell tests showed no significant between group differences on processing speed (supplementary materials 1).

*Adolescent cognitive and behavioural responses to symptoms*

One-way ANOVA demonstrated a significant main effect of group on all subscales of the CBRQ (Table 4). Post-hoc tests showed that fatigued caMS reported significantly greater catastrophising ($p$ = .004), and all-or-nothing behaviour ($p$ = .002) than healthy controls, but did not significantly differ to adolescents with CFS or non-fatigued caMS on any CBRQ subscale (Figure 2). Adolescents with CFS reported significantly higher catastrophising, damage beliefs, embarrassment avoidance, symptom focusing, all-or-nothing behaviour, avoidance-rest behaviour (all $p$ < .001) and fear avoidance ($p$ = .002) than healthy controls, and reported significantly greater symptom focusing ($p$ = .008) and embarrassment avoidance ($p$ = .003) than non-fatigued caMS (supplementary materials 1).

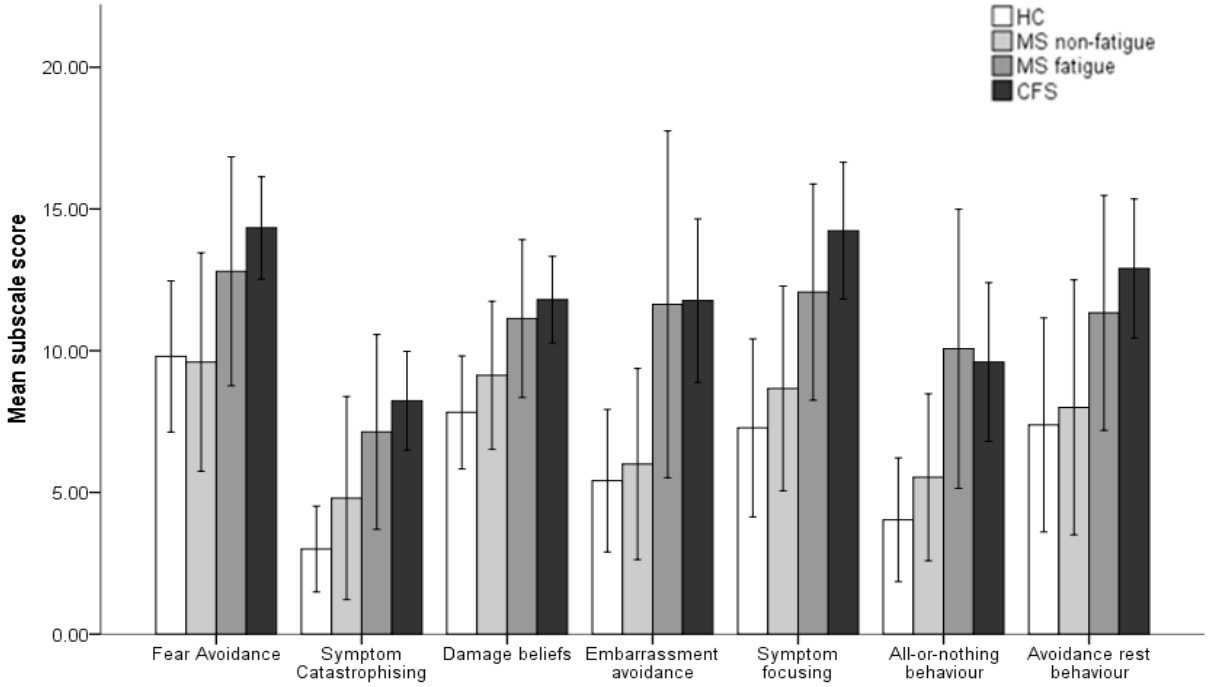


*Figure 2.* Group differences in mean subscale scores on the adolescent Cognitive and Behavioural Responses to Symptoms Questionnaire. CFS = Chronic Fatigue Syndrome, HC = healthy controls.

*Parent cognitive and behavioural responses to symptoms*

One-way ANOVA demonstrated a significant main effect of group across all measures of parents' cognitive and behavioural responses to their children's symptoms (Table 5). Post-hoc Tukey tests showed that parents of fatigued caMS and adolescents with CFS reported significantly higher fear avoidance beliefs, damage beliefs and catastrophising than parents of healthy controls, and parents of adolescents with CFS reported significantly higher fear

avoidance beliefs than parents of non-fatigued caMS (all $p<.001$). Parents of non-fatigued caMS reported significantly higher damage beliefs ($p<.001$) and catastrophising than parents of healthy controls (all $p=.008$).

*Sleep*

Mean physiological arousal, cognitive/emotional, sleep environment and daytime sleepiness scores indicated that adolescents in all groups generally engage in positive sleep behaviours. However, on the behavioural arousal and sleep stability subscales, mean scores suggested that adolescents in all groups may engage in behaviours that inhibit sleep. One-way or Welch's ANOVA demonstrated no significant main effect of group on any sleep variable, except for daytime sleepiness (Table 4). Games-Howell post-hoc tests indicated no significant differences between groups at the $p < 0.01$ level. At the $p < 0.05$ level, fatigued caMS had significantly higher daytime sleepiness scores than non-fatigued caMS and healthy controls, and adolescents with CFS had significantly higher scores than healthy controls.

*Internalising and externalising difficulties*

Welch's ANOVA demonstrated a significant main effect of group on the internalising difficulties, but not on the externalising difficulties subscale of the SDQ (Table 4). Post-hoc Games-Howell tests found no significant between group differences in internalising difficulties (supplementary materials 1).

*Parental Distress*

Mean psychological distress scores were elevated in parents of fatigued caMS and parents of adolescents with CFS, while parents of non-fatigued caMS and healthy controls all scored within the normal range on the GHQ-12. One-way ANOVA demonstrated a significant main effect of group on parental distress (Table 5). Post-hoc Tukey tests showed greater parental distress in the CFS group when compared to healthy controls ($p = .006$), but found no other significant differences between groups.

**Discussion**

This study provides a novel insight into fatigue, psychosocial factors and cognitive functioning in children and adolescents with MS, CFS and without a chronic illness. Fifty

percent of caMS in our sample reported clinically significant fatigue. Fatigued caMS reported similar levels of fatigue severity to adolescents with CFS on both self- and parent-report measures, with high agreement between self- and parent reports. Both fatigued groups reported similar levels of functional impairment, which were higher than in the non-fatigued groups, highlighting the disabling nature of fatigue. Adolescents with CFS had the lowest school attendance. School attendance did not significantly differ between adolescents with CFS and fatigued caMS, suggesting that reduced school attendance is also problematic for fatigued caMS. Consistent with previous paediatric and adult MS literature, this study found no clinical or demographic differences between fatigued and non-fatigued caMS, but indicated some possible parallels between psychosocial factors in fatigued caMS and adolescents with CFS.

This was the first study to quantitatively explore cognitive and behavioural responses to symptoms in caMS and their parents. There were no differences between fatigued caMS and adolescents with CFS in cognitive and behavioural responses to symptoms, and fatigued caMS reported higher all-or-nothing behaviour and symptom catastrophising than healthy controls. This echoed recent qualitative data where fatigued caMS described engaging in all-or-nothing patterns of behaviour in response to fatigue, and feeling that fatigue was uncertain and uncontrollable (Carroll et al., 2016a). Both these factors have previously shown associations with fatigue in adult MS and adolescent CFS, and strategies directed at modifying these behaviours and cognitions have been incorporated into CBT based interventions for fatigue (Chalder et al., 2010; Moss-Morris et al., 2012). As previous literature on adolescent CFS has informed the development of effective interventions for adolescent fatigue, the similarities identified between fatigued caMS and adolescents with CFS offer new insights into paediatric MS fatigue, and highlights potential targets for tailored interventions for caMS with fatigue.

Notably, there were no significant differences between fatigued and non-fatigued caMS on adolescent cognitive and behavioural responses to symptoms, although descriptive data suggested that responses of fatigued caMS were closer to those of adolescents with CFS, while responses of non-fatigued caMS appeared closer to those of healthy controls. The sample sizes may have been too small to detect differences between the MS groups. However, it is worth considering that non-fatigued caMS may also engage in unhelpful cognitive and behavioural responses to symptoms not specific to fatigue, as they likely

experience other MS symptoms similar to fatigued caMS. Therefore, it may be useful to explore these factors in the wider context of adjustment and symptom management in paediatric MS, rather than solely in a fatigue-specific context.

This was reflected in parents' cognitive behavioural responses to symptoms, as parents of all illness groups reported significantly higher damage beliefs and catastrophising than parents of healthy controls, indicating that parents' cognitive behavioural responses to symptoms are similar regardless of fatigue. It should be acknowledged that caMS and adolescents with CFS experience more severe and serious symptoms than healthy controls, thus it is natural for parents to have greater concerns. However, fear avoidance beliefs appeared to be specific to parents in the fatigue groups, suggesting that parents of fatigued caMS and adolescents with CFS have greater concerns about exercise and activity when their children experience symptoms. As exercise and activity have been shown to benefit adults with MS fatigue and adolescents with CFS, addressing parents' fear avoidance beliefs may be an important target for intervention.

It was notable that fatigued and non-fatigued caMS did not significantly differ on any domain of neurocognitive functioning or full scale IQ. Non-fatigued caMS, but not fatigued caMS, had lower perceptual reasoning, verbal comprehension and full scale IQ scores compared to adolescents with CFS and healthy controls. Though the MS sample sizes may have been too small to detect differences between groups, these findings suggest that impaired cognitive functioning is problematic for caMS regardless of fatigue. Mean scores across all domains of neurocognitive functioning indicated that a substantial proportion of caMS scored in the low average, borderline or extremely low range compared to population norms. As impairment in neurocognitive functioning has the potential to significantly impede caMS' school performance and future academic attainment, supporting caMS with neurocognitive impairment should be prioritised in schools and clinical practice. In line with previous studies' recommendations, incorporating regular neuropsychological assessments as part of routine care is key to supporting caMS in a clinical context (Amato et al., 2014).

Parental distress differed between groups, although the same was not true for adolescents. Parental distress was significantly higher in parents of adolescents with CFS than in parents of healthy controls and mean scores indicated elevated distress in parents of fatigued caMS, supporting previous studies in adolescent CFS which highlighted the

importance of measuring parental distress in the context of fatigue. As this study was cross-sectional, causality cannot be inferred from our findings. However, functional impairment in school and recreational activities in fatigued caMS could be quite distressing for parents. Alternatively, parental distress could contribute to children's fatigue.

Finally, this study offered interesting insights into adolescent sleep behaviour. Although there were no significant differences between groups on any sleep variable, mean scores of all groups indicated that adolescents may regularly engage in unhelpful sleep behaviours, particularly regarding sleep stability and behavioural arousal. Trends in the data suggested that fatigued caMS had higher daytime sleepiness than non-fatigued caMS and healthy controls, but did not differ from adolescents with CFS, indicating that adolescents with fatigue nap more during the day. As daytime napping, irregular sleep patterns and activities such as using phones or watching television before bed can all contribute to fatigue and negatively impact health, it would be useful to explore these factors in future research (Owens, 2014). These factors may be important potential targets both for interventions in the wider context of adolescent sleep behaviour, and interventions for fatigued caMS.

## Limitations

The study is limited by its small sample, particularly where separating caMS into fatigued and non-fatigued subgroups resulted in smaller groups. It's possible that the study was underpowered to detect between-group differences in some variables. There were missing neurocognitive data, which limits the conclusions that can be drawn from between-group comparisons of neurocognitive functioning. Though the p-value was adjusted to reduce the type 1 error risk, this study was also limited by the number of comparisons conducted. Participants in our sample were recruited from specialist services. Attempts were made to contact all relevant patients in these services but not all patients provided informed consent. Others were recruited through online platforms where participants opted in to the study. As for ethical reasons we were unable to collect data on the differences between those who participated and those who did not, our sample may not be representative.

## Conclusions and Future Directions

Fatigue is clearly a significant issue for 50% of caMS in our sample, and intervention for this symptom is much needed. Similarities in adolescents' and parents' cognitive and

behavioural responses to symptoms between fatigued caMS and adolescents with CFS suggest that it may be useful to tailor existing CFS cognitive behavioural interventions for caMS and their parents. Interventions should target these similar factors, and factors previously associated with paediatric MS fatigue, such as managing school and issues around disclosure of MS and fatigue. It would be beneficial to routinely screen for fatigue in caMS in clinical practice so that timely intervention may be offered when it is problematic. This study also highlighted impaired cognitive abilities in caMS regardless of fatigue, highlighting the need to routinely assess neurocognitive functioning in clinical practice so appropriate support may be provided. As paediatric MS is rare, which makes it difficult to address the problem of small sample sizes, future research would benefit from adopting a collaborative multi-centre international approach to obtain sample sizes large enough to conduct more in-depth studies.

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